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Contents

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Statement of Purpose:
AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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safety, and efficacy information about a new drug, starting with the first volunteer who takes it.

Retroviruses Conference Date Set.....

The 2005 Retroviruses conference will be February 22-25 in Boston.

HIV Treatment and Immunology Research: Current Ideas.....

Here are some leading scientific ideas for developing new kinds of HIV treatments.

Chronically Depressed Women with HIV Almost Twice As Likely As Others to Die from AIDS-Related Causes; Those with Mental-Health Services Had Half the Death Rate of Those Without

by John S. James

A study of 1,716 HIV-positive women who were given blood tests and interviews twice a year for seven years from 1994 through 2001 found that those who met research criteria for chronic depressive symptoms were 2.2 times as likely to die of AIDS-related causes as those who were not depressed. (1) After statistically controlling for CD4 count, viral load, aids-related symptoms, HAART or other antiretroviral use, cocaine or heroin use, income level, age, race, and other factors, those who were chronically depressed still were 1.7 times as likely as those who were not to die of AIDS-related causes. Interestingly, "intermittent" depression symptoms had no effect on death rate in this study. Also, HAART treatment itself was associated with less depression.

Those who used mental-health services

at any time during this study (about two thirds of the volunteers) were only half as likely to die as those who did not -- with or without statistical correction for all the other factors.

In addition, this study found that women who died from AIDS-related causes were about twice as likely as HIV-positive women who did not die to report clinically significant depression in their last two 6-month visits.

This study analyzed data from the Women's Interagency HIV Study (WIHS), from volunteers' visits to clinics in Brooklyn, Bronx, Chicago, Los Angeles, San Francisco, and Washington DC.

The authors believe that "antiretroviral therapy alone does not meet best-practice standards of care for this population, and therapy must be augmented by appropriate and sensitive mental health treatment, particularly as HIV disease progresses. Thus, finding ways to reduce depressive symptoms has the potential not only to prolong life but also to enhance its quality among women who have HIV."(1)

Comment

Evidence increasingly suggests that treating "mental" illness or distress can improve survival and reduce progression of HIV (and some other diseases) -- not only in obvious ways like improving adherence and social support, but also through biochemical mechanisms that researchers are only beginning to understand. If confirmed, this emerging information could lead to one or more new classes of HIV treatment. These new treatments would probably target human instead of viral biochemistry, probably greatly reducing the development of viral resistance. Available information suggests that they might have a large effect on disease outcome, not a small or marginal one. And some might already be on pharmacy shelves, approved for other purposes with their value for HIV unrecognized.

The new report(1) is consistent with many studies that have found that depression is associated with worse outcome in HIV and other diseases -- and with growing indications that treatment of "mental" conditions can make a big difference in the progression and outcome of the "physical" illness. *AIDS Treatment News* reported on one of these studies that was published last December ("'Shy' Study Suggests New Treatment Mechanism," *AIDS Treatment News* #397, December, 2003). This careful research in 54 HIV-positive men(2) found that the HIV viral load set point was eight times higher in people with a high anxiety level -- who also responded less well to antiretroviral treatment, with only about one-eighth the reduction in viral load of other patients, when both began HAART for the first time. Also see Evans 2002(3): "Our findings provide the first evidence that depression may alter the function of killer lymphocytes in HIV-infected women and suggest that depression may decrease natural killer cell activity and lead to an increase in activated CD8 T lymphocytes and viral load" (quote from the abstract).

For reviews, see Cruess 2003(4) and Leserman 2003(5) on depression and stress in HIV; also see Herbert 1993(6) on stress and immunity in humans. And an excellent newspaper article appeared last December in *The Washington Post*. (7)

The impact of mental health treatment on disease progression and survival needs more attention from doctors, researchers, policy makers, and activists alike. Activists could help by becoming informed, mobilizing public support for research, and supporting the inclusion of

mental-health services in HIV medical care.

Ongoing attention and conversation could lead to research that may provide new treatments to reduce HIV disease progression. *AIDS Treatment News* will follow this area, and suggest ways that readers can help.

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Cambodia Stops Important Tenofovir Prevention Trial

by John S. James

On August 11, 2004, the Cambodian government ordered researchers not to proceed with a trial to test whether once-daily use of tenofovir (brand name VIREAD), a drug already widely used to treat HIV, could prevent new infections in healthy people. The government had previously approved the study, which is funded primarily by the U.S. National Institutes of Health and the Bill & Melinda Gates Foundation. A Cambodian organization of sex workers had protested the trial, which was to recruit HIV-negative sex workers at high risk of infection, primarily because it did not include at least 30 years of insurance in case of side effects from the drug.

On August 15 I sent the following to ACT UP Philadelphia and other U.S. activists, to explain why this research is important.

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Stopping this trial is a serious setback to controlling the epidemic. The new prevention method being tested could save millions of lives if it works. Fortunately the study is being run not only in Cambodia but in other countries as well.

Experts say they will not have an HIV vaccine for at least ten years. Tenofovir (brand name Viread, from Gilead Sciences in California), the drug that was to be tested in Cambodia, is already in widespread use for treating HIV, so it is available now. In a small monkey study, an injectable form of tenofovir gave

100% protection against infection by SIV (simian immunodeficiency virus, which is like HIV). All the monkeys were deliberately exposed to SIV -- and every monkey that got tenofovir was protected, while all the others in the no-treatment control group became infected (*Science*, November 17, 1995, volume 270, page 1197).

If tenofovir works anywhere nearly this well in people, it could be at least as effective for preventing HIV as a vaccine. The drawback would be the need to take a pill once a day. So there could be a vaccine already for people at high risk, who might choose protection at the cost of the inconvenience and risk of side effects. Epidemiologists could watch where the epidemic is going and offer free drug to those most likely to become infected, for example, sex workers -- protecting not only them, but many others who could have been infected directly or indirectly through them. This new prevention tool, if used well, might possibly be enough to control the epidemic. But it won't be used at all unless it can be tested first.

If it works, tenofovir will be a form of prevention that women could control. They would not need to get men to put on condoms, nor tell men that they are using protection against HIV. And for both men and women, this kind of prevention would not require people to change their sexual behavior -- avoiding a major obstacle to the effectiveness of HIV prevention today. (Not much in human life is perfect, so behavior change will also be needed as well.)

Tenofovir has been approved as an HIV treatment for over two years in the U.S. and Europe, and has become widely used because it is one of the safest HIV drugs. The dose planned for the prevention trial is the same as that used for treatment. In an early study of tenofovir, eight volunteers took twice this dose for 28 days with no adverse effects. Almost all the experience with tenofovir so far has been in HIV-positive patients and volunteers -- but healthy, uninfected persons have if anything less problem with drug side effects than those who have HIV or other illness.

The group that objected to the trial, the Women's Network for Unity, "was established in June 2000 by a group of sex workers for sex workers," and says it has 5,000 members in Cambodia. Women's Network for Unity protested the tenofovir trial at a press conference in Phnom Penh on March 29, 2004, because the trial does not include insurance to treat drug side effects that may continue after the trial. It also protested at the Bangkok conference, with the support of ACT UP Paris. It appears to be an excellent organization; for more information, see
http://www.swop-usa.org/world%20news/Cambodian_news.html

The demand for 30 years insurance is the main issue fueling the protests. There has been confusion in the press, with some researchers thinking the demand is for 30 year of general health care -- a large incentive that would raise ethical objections that participants were not consenting voluntarily to the trial. But from what I have seen in news reports, Women's Network for Unity only asked for treatment of any side effects of the drug being studied -- which is not an incentive to join the trial, so it does not raise questions of undue incentive interfering with voluntary consent.

Of course sponsors of clinical trials would worry about an arrangement that might give volunteers or their doctors 30 years of payments if they said the experimental drug made them sick.

Often nobody knows the cause of an illness; a powerful incentive to blame the drug would not only raise the cost of doing a trial but, much worse for the sponsor, could affect the result, making any drug look more dangerous than it is. Probably for this reason, it is common practice in the United States to *not* guarantee medical care beyond the trial for side effects of the study drug. But U.S. volunteers have more access to medical care outside the trial than those in most poor countries.

The tenofovir prevention trial was developed collaboratively to meet current ethical standards. It passed ethical review in every country involved (unfortunately, many trials in developing countries do not). And if the drug is found to be effective for preventing HIV infection, all volunteers will be offered it free for two years after the trial, by which time other programs should be in place to supply it. The main issue that led to stopping this trial in Cambodia could affect any clinical trial in poor countries where people cannot get modern medical care.

Hopefully these issues can be resolved satisfactorily. Many people may live or die depending on whether the tenofovir HIV prevention trials are completed.

John S. James, *AIDS Treatment News*

Hepatitis Coinfection: Two Major Studies Published

Two large clinical trials on treating hepatitis C in patients also infected with HIV(1,2) were published July 29, 2004, in the *New England Journal of Medicine*. The results were already known because they had been presented at the 2004 Retroviruses conference (abstracts #110 and #112). The new publication provides much more detail -- and more credibility when it is necessary to advocate for payment from insurance companies or public agencies (including prisons) for patients with HIV who need treatment for hepatitis C (many who have hepatitis C do not need treatment, at least not immediately). Often two articles in peer-reviewed journals are demanded by payers to establish that a treatment is standard of care (meaning that refusing to consider it is probably malpractice). Now we have the two articles -- in the medical journal usually considered the most prestigious in the U.S.

An August 4 summary by AIDS writer Liz Highleyman, "Final APRICOT and ACTG 5071 HIV/HCV Coinfection Results Published," is available at Aidsmap, http://www.aidsmap.com (try searching for APRICOT). This is a place to start for understanding these trials and what they mean for treatment of hepatitis C.

An editorial in the Perspective section of the same issue of *New England Journal of Medicine*, "Treating Hepatitis C in 'Difficult-to-Treat' Patients" includes important background about the disease, causes of treatment failures, and prospects for major improvement in hepatitis C treatment over the next five to ten years. The text of this editorial is at
http://www.natap.org/2004/HCV/080404_02.htm

The abstracts of the two studies are available at
http://content.nejm.org/content/vol351/issue5/index.shtml

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APRICOT study.]

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FDA Approves Two Combination Pills, Epzicom and Truvada; Comment on Commercial Race to Once-a-Day Nucleosides

by John S. James

On August 2, 2004, the U.S. FDA approved once-daily combination antiretroviral pills from two companies: GlaxoSmithKline's Epzicom (Ziagen [abacavir] + Epivir [3TC]), and Gilead Sciences' Truvada ([Viread [tenofovir] + Emtriva [FTC]). Both are taken once a day, combined with other antiretrovirals NOT part of the nucleoside/nucleotide class. Truvada was given accelerated approval (which means that Gilead must complete additional work) because approval was based in part on clinical trials of Viread with 3TC -- a drug similar to FTC but not the same. Epzicom received final approval on August 2.

Since both ingredients of each combination were previously approved in the U.S., these new approvals reduce the pill count, but do not create new medical options for patients. They may ease financial burdens for some, because there is only one "prescription" instead of two, reducing some co-pays -- and helping to meet some health plans' arbitrary limits on the number of prescriptions a patient can have at any one time.

Glaxo will provide a limited number of waivers to physicians, allowing patients to obtain free Epzicom in order to give their health plans time to include it in coverage. We do not have details of this program.

An FDA press release on these approvals is at
http://www.fda.gov/bbs/topics/news/2004/NEW01099.html

Because Epzicom contains Ziagen, all the precautions about drug hypersensitivity reactions to Ziagen must be followed. This reaction may be more common with once-daily dosing; a study in 770 patients found more cases of severe hypersensitivity in the group that took all the medicine once per day, instead of taking it in divided doses twice per day (5% of the once-daily Ziagen group had severe hypersensitivity, vs. 2% of the twice-daily group -- see Epzicom and Ziagen prescribing information for doctors. Epzicom is dosed for once-daily use only. If hypersensitivity occurs, Epzicom (or any other form of Ziagen) must be stopped and NEVER restarted. Glaxo has prepared material to help patients recognize when this reaction might be occurring, so that they can talk with their doctor immediately about how to proceed.

Comment: Concern on the New Once-Daily Nucleosides

AIDS Treatment News is concerned that commercial competition could drive a rush to once-a-day regimens that include the nucleoside/nucleotide class of drugs, without enough attention to what is best for each patient. Some issues need more thought before there is a mass switch for the convenience of

once a day.

One problem is the hypersensitivity danger with abacavir, mentioned above. The traditional twice-daily nucleoside drugs do not cause this reaction.

Also, two three-drug regimens that doctors agree should *never* be used as the only antiretroviral treatment are tenofovir plus 3TC plus abacavir, or tenofovir plus 3TC plus ddI; these were unexpectedly found to cause serious drug resistance in many cases, including the K65R and M184V/I mutations. The problem was seen in regimens *without* AZT, which doctors have noticed helps to prevent this kind of resistance. We are concerned that the newly approved combinations are too close to comfort to a part of the failed 3-drug regimens, and are intended to be used only without AZT.

The new combinations may well be successful, and some patients will benefit. But we are not convinced that all the questions have been answered well enough to justify a wholesale switch, just because once a day is spun as the thing to do, in direct-to-consumer advertising. The FDA approved both combinations on the same day -- which is "fair," but could lead to a horse race between the two companies' products that may not be in the public interest.

Smarter Clinical Trials for Faster Drug Development

An August 4 *New York Times* article describes a new approach to clinical trials. The idea, (sometimes called "experimental medicine") is to use modern imaging, genetic, and other technology early, starting with the first patient who ever takes an experimental drug, to get solid indications of whether or not it is working. Researchers and companies make sure the drug is getting to where it is needed in the body, that it has the biochemical effects intended, and that the dose is appropriate -- eliminating losers early and focusing attention and resources on more promising drug candidates. The traditional approach uses the first human trials to pick the largest dose most patients can tolerate (which may be more than needed for medical efficacy, but is likely to become a standard dose for further research and for approval), and only then runs other trials to start testing whether the drug does anybody any good.

Comment

AIDS is barely mentioned in the article -- perhaps because it is no longer in the forefront of clinical-trial design. In AIDS and other diseases the biggest block to finding new treatments seems to be the gap between where academic research stops and where drug development begins. Many good ideas get published in journals, but usually the researchers who developed them do not do human testing, and no one does the next, relatively inexpensive steps to show which ideas have solid potential for practical development now. And usually only one company has the legal rights to a compound, so if anyone else has a good idea for using it, they (and the public as well) are often out of luck. Or nobody has exclusive rights, so no company gets involved. Clearly the current system works very poorly in turning scientific advances into new kinds of treatment, and fundamental rethinking is needed.

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